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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BRISTOL, LYNN ANNE	
ART UNIT	**PAPER NUMBER**
1643	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/16/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/542,839	KOJIMA, TETSUO	
	Examiner	Art Unit	
	Lynn Bristol	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *8-12 and 16-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 13-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/14/06; 12/21/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-18 are all the pending claims for this application.

2. The amendment to the specification of 7/20/2005 has been considered and entered.

Election/Restrictions

3. Applicant's election without traverse of Group I (Claims 1-7 and 13-15) in the reply filed on 1/3/07 is acknowledged.

Claims 8-12 and 16-18 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions of Groups II and III, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 1/3/07.

4. Claims 1-7 and 13-15 are all the pending claims under examination for this application.

Information Disclosure Statement

5. The international and foreign patent references and the non-patent literature references cited in the IDS' 4/14/06 and 12/21/06 have been considered and entered.

Oath/Declaration

6. The oath or declaration is defective because:

Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

Specification

7. The disclosure is objected to because of the following informalities:

a) Page 1 of the specification contains non-initialed markings. A replacement page is required.

b) The arrangement of the specification is objected to because the section entitled "Brief Description of the Drawings" on p. 14 should be inserted between the section for the "Background of the Invention" and the "Detailed Description of the Invention".

c) The legends for Figures 1 and 2 are objected to because they not describe in sufficient detail the depictions in the figures. MPEP 608.01(f) and 37 CFR 1.74. For example, identifying and explaining each abbreviation (both Figures 1 and 2) and the steps involved in the process (Figure 2) would overcome this objection.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1-7 and 13-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a) Claims 1-7 and 13-15 are indefinite for the recitation "screening for commonly shared light chains" because in Claims 1 and 2, it is not clear what molecule or structure is being claimed. Several immune and non-immune related molecules are comprised of a light chain such as for example, antibody light and heavy chain, myosin light and heavy chain, heavy-chain and light-chain L ferritin, clathrin light and heavy chain, etc.

Further the phrase "commonly shared" in claims 1 and 2 renders the claim indefinite. The phrase is not defined by the claim, the specification does not provide a standard for ascertaining what the commonality should be, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Should the same or different molecules have two or more light chains, and if so, what degree of homology, identity or similarity should occur between the light chains to constitute the light chains being shared? What is a "commonly shared" light chain?

b) Claims 3 and 13 recite the limitation " the antibody heavy chain is Fd". There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

9. Claims 1, 2, 4-7, 14 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carter (J. Immunol. Methods 248:7-15 (2001); cited in the IDS of 4/14/06) in view of Winter et al. (US2004/0219643; published 11/4/04; priority filing date 6/28/02; cited in the 892 form of 12/7/06).

Claims 1, 2, 4-7, 14 and 15 are drawn to methods for screening bispecific antibodies having a commonly shared light chain using phage display libraries in E. coli, where a heavy chain-antigen-selected library is introduced into a host and a light chain library is further introduced, and the antibody is selected for the antigen, where the selected antibody is introduced into a second host comprising a heavy chain-antigen selected library where the antigen is different from the first antigen, or where the heavy chain sequences are different from the first library (Claim 2) and selecting antibodies that bind to the first and second antigen and share the same or a similar light chain, and where the steps are repeated twice or more.

The invention for screening bi-specific antibodies sharing a common light chain was prima facie obvious at the time the invention was made over Carter and Winter.

Carter discloses in general that in order to limit the occurrence of the formation of incorrect combinations of pairs of heavy chains and light chains so that efficient production can be achieved when producing bispecific antibodies having two different heavy chains, a common light chain is used that can be combined with either of the two heavy chains. Moreover, when selecting the common light chain, a search is performed for an antibody having a light chain comprising an amino acid sequence that is identical to or similar to both the groups of antibodies having one of two heavy chains and the groups of antibodies having the other heavy chain, the light chain of the antibody is used as the light chain. Carter discloses using a common light chain that can be combined with either of two heavy chains so that efficient production of bispecific antibodies can be achieved. Carter does not disclose a screening method where host cells secrete a heavy chain, a light chain is introduced into the host cell, a phage library presenting antibodies comprising heavy and light chains is prepared, and the library is selected that presents the antibodies having heavy chains uniquely bonding with different desired antigens, which is used when performing this multi-step screening. Winter rectifies these deficiencies in its disclosure.

Winter discloses methods for producing dual-specific IgG antibodies having two VH/VL pairs, one pair on each arm of the antibody where the method involves a) selecting a first variable domain by its ability to bind to a first epitope expressed from a phage display library, b) selecting a second variable region by its ability to bind to a second epitope expressed from a phage display library, c) combining the variable regions into a construct for expression by the same host; and d) selecting the dual-

specific ligand by its ability to bind to said first and second epitopes expressed from a phage display library. Winter discloses antibodies (Fab) produced by phage antibody library methods where all the antibodies share or have in common the same VL domain or light chain for anti-beta galactosidase; specifically antibodies for anti-(HSA) (VH, heavy chain)/anti-beta galactosidase (VL, light chain) (Example 1) and anti-APS (VH, heavy chain)/anti- beta galactosidase (VL, light chain) and anti-BCL 10 protein (VH, heavy chain)/anti-beta galactosidase (VL, light chain) (Example 3). The specification discloses a very specific method of screening human phage antibody libraries in E. coli based on a single human framework for VH (V3-23/DP47 and JH4b) and Vκ (O12/02/DPK9 and Jκ1) with side chain diversity incorporated in complementarity determining regions (CDR2 and CDR3), identifying ligands which bind to different antigens, but have identical Vκ domains (anti-βgal), and selecting those to combine in production of a dual specific ligand, for the purpose of increase yield of functional dual-specific ligands.

One skilled in the art would have been motivated to have produced the screening method for identifying commonly shared light chains for bi-specific antibodies and been assured of success in doing so based on the combined disclosures of Carter and Winter. Carter discloses bispecific antibodies in which the binding of a first antigen or epitope does not necessarily facilitate the binding of a second antigen or epitope, and that the solution lies in creating binding contacts for the first antigen or epitope in one variable domain, and binding contacts for the second antigen or epitope in another variable domain, where the domains are selected so that they are mutually

complementary, and Winter discloses the technology for expressing and selecting heavy and light chains or more specifically VH and VL domains expressed by phage display libraries, and combining selected binding pairs with other selected binding pairs in the same host to express bispecific antibodies sharing the same or common light chain or VL domain. One would have been assured of success in producing the instant claimed method because methods for screening for antigen binding specificity for one group by performing searches or screening, and then performing a second search from the first selected antibody to identify antigen binding specificity for a different antigen of the second group was within the ordinary skill of the artisan and taught by Carter. Further, because Winter discloses the technology using phage display libraries in screening antibodies with dual-specificity and where the dual specific ligand may be combined into full antibodies or Fabs, one skilled in the art could readily have modified the method of Carter based on the methods of Winter to obtain the instant claimed method.

For all of the foregoing reasons, the claims were prima facie obvious over Carter and Winter at the time the claimed invention was made.

10. Claims 1-3 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carter and Winter as applied to claims 1 and 2 above, and further in view of Goldstein et al. (J. Immunol. 158:872-879 (1997)).

The interpretation of Claims 1 and 2 is discussed supra. Claims 3 and 13 are drawn to the method where the heavy chain of an antibody is Fd and the antibody composed of heavy and light chains is Fab.

The method using a Fd fragment for the heavy chain in a method for producing a bispecific Fab antibody was prima facie obvious at the time the invention was made over Carter, Winter and Goldstein.

The interpretation of Carter and Winter is discussed supra. Neither reference alone or in combination teach using a Fd fragment as the starting material for the heavy chain in a method for producing bispecific Fab antibody having a commonly shared light chain. Goldstein rectifies this deficiency in its disclosure.

Goldstein discloses a method for producing a bispecific fusion protein comprising a Fab linked to an EGF molecule where the starting material for the heavy chain was an Fd fragment from a humanized antibody and the Fd fragment was linked to EGF, where upon transfection into a host cell (myeloma) further comprising the kappa light chain for the humanized antibody, the Fab'-EGF monomer was secreted. Goldstein teaches efficient expression of the molecule.

One skilled in the art would have been motivated to have produced a method for screening commonly shared light chains in a bispecific antibody where the heavy chain was a Fd and the antibody composed of the heavy and light chain was a Fab on the basis of the combined disclosure of Carter, Winter and Goldstein. Carter and Winter provide the motivation for making improved bispecific antibodies and methods for producing these molecules, and given the desirability of using smaller sized fragments

that retain the full binding characteristics of the parent antibody, one skilled in the art would have been motivated to have used an Fd fragment as taught by Goldstein, because Goldstein teaches fusion methods, assembly of the Fd fragment with the light chain, and antigen specificity for the fragment upon assembly. One skilled in the art would have been reasonably assured of success in producing a screening method based on these disclosures because the technology was available to perform the steps to produce each of the different molecules on a step-wide basis according to the instant claimed method, and because bispecific antibodies sharing a common light chain were already known in the art based on the disclosure of Carter and Winter and that Fd fragments could be used in bispecific fusion proteins which resulted in successful assembly of the Fab into a functional, antigen-binding fragment based on Goldstein.

For all of the foregoing reasons, the claims were prima facie obvious at the time the invention was made in view of Carter, Winter and Goldstein.

Conclusion

11. No claims are allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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